Online Supplement

Original Research

Comparison of Nebulized Long-Acting Muscarinic Antagonist Revefenacin to Ipratropium in COPD Patients With Acute Respiratory Failure Requiring Mechanical Ventilation: Results of the RARICO Study

Igor Barjaktarevic, MD, PhD[1*] Matthew Dartt, MBA, BSRT, RRT-ACCS[2] Siyan Chen, MS[3] D'Mitri Champion, RRT[2] Roberto Mempin, MD[1] Yongyus Dejsatha, RRT[2] Joseph Van Vleet, BSRC, RRT[2] Steven Chang, MD, PhD[1] Oscar Estrada, MD[1] Timothy Young, MD[1] Russell Buhr, MD, PhD[1] Donald Tashkin, MD[1] Joanne M. Bando, MD[1]

[1] Division of Pulmonary and Critical Care Medicine, David Geffen School of Medicine, University of California Los Angeles, Los Angeles, California, United States

[2] Respiratory Care, University of California Los Angeles, Los Angeles, California, United States

[3] Biostatistics, University of California Los Angeles, Los Angeles, California, United States

Supplemental Table 1: eligibility criteria

Inclusion criteria

Adults ≥ 40 years of age

Acute respiratory failure requiring invasive mechanical ventilation

Documented history of COPD based on spirometry with percent predicted post bronchodilator $FEV_1/FVC<70\%$

Smoking history ≥10 years (current or prior)

Invasive mechanical ventilation for ≤ 96 hours

Exclusion criteria

Chronic invasive mechanical ventilation via tracheostomy. Patients with tracheostomy alone without chronic mechanical ventilation may be enrolled.

Expected duration of mechanical ventilation <24 hours

Hypersensitivity to muscarinic antagonists

Persistent inability to tolerate albuterol

Lack of documented COPD history

For patients taking short- or long-acting muscarinic antagonists (SAMAs or LAMAs) at the time of screening, inability or unwillingness to undergo the SAMA or LAMA washout period (6 hours or 24 hours, respectively) prior to initiating study drug.

Presence of severe ARDS defined by P/F ratio<150 at the time of enrollment

Unwillingness or inability to remain on the study drug with for the duration of the study

Unwillingness or inability to utilize the Puritan-Bennett 980 (PB980) ventilator

Pulmonary comorbidities such as pneumothorax or pneumomediastinum that, in the opinion of the investigator or clinical team, can pose a risk to subject safety or interfere with the subject's ability to complete the study procedures.

Clinically significant diagnosed restrictive lung disease

Actual body weight exceeding 1 kg per centimeter of height

Pregnancy

AST or ALT > 3 times the upper limit of normal, or other clinically significant acute or chronic liver disease

Known history of narrow-angle glaucoma

Enrollment in other interventional clinical trial

Moribund patient not expected to survive >24 hours

Decision to withhold life-sustaining treatment, except in those patients committed to full support except cardiopulmonary resuscitation

Inability to obtain informed consent from patient or legally authorized representative (LAR)

Supplemental Table 2: Definition of mechanical ventilation-related outcomes:

Static compliance (C_{stat}) is an estimate of the elasticity of the patient's respiratory system; it is expressed in mL/cmH2O.

C_{stat} is computed from this equation

$$C_{STAT} = \frac{V_{EXH}}{P_{PL\ END} - PEEP} - C_C$$

Static resistance (R_{stat}) is the total inspiratory resistance across the artificial airway and respiratory system. It is an estimate of how restrictive the patient's airway is, based on the pressure drop at a given flow; it is expressed in cmH2O/L/second. These values are computed during an operator-initiated inspiratory pause, in which the PSOL valves and exhalation valve are closed. R_{stat} is computed during a mandatory breath. R_{stat} is computed during a VC mandatory breath with a square waveform.

$$R_{STAT} = \frac{[1 + \frac{C_C}{C_{STAT}}] \quad (P_{PEAK} - P_{PL\ MID})}{\dot{V}_{PAT}}$$

Dynamic resistance (R_{dyn}) indicates the impedance characteristics of the lungs, chest wall and conducting airways. It is expressed in cmH2O/L/second on breath to breath basis in assisted control ventilation mode.

Peak Pressure (P_{peak} or PIP) is the maximum pressure measured during the inspiratory phase of the current mandatory or spontaneous breath and is updated at the end of each inspiration. The ventilator displays negative P_{peak} values. The ventilator displays the most positive value of the low-pass filtered airway pressure measured during the inspiratory phase. P_{peak} can be used to evaluate trends in the compliance and resistance of the respiratory system.

Plateau Pressure (P_{pl}) is the pressure measured in the ventilator breathing circuit at the end of an inspiratory pause maneuver. Because the pause maneuver is conducted with the ventilator breathing circuit sealed (PSOL valves and exhalation valve closed and assuming a leak-tight system), is the best estimate of the pressure in the patient's lungs. Beginning with the start of the pause maneuver, P_{pl} is displayed and updated continuously. At the end of the maneuver, along

with the other pause data P_{pl} is “frozen,” enabling you to view all of the data together. Pressing “UNFREEZE” causes the data to be discarded.

Resistive pressure (P_{res}) in mechanical ventilation is the pressure needed to overcome airflow resistance in the ventilator circuit, endotracheal tube, and the patient's own airways (like bronchioles), representing the difference between peak inspiratory pressure (P_{peak}) and plateau pressure (P_{plat})

End expiratory pressure (PEEP) is the pressure measured at the end of the exhalation phase of the just completed breath, whether mandatory or spontaneous. The accuracy of the PEEP measurement is dependent of the engagement of expiratory muscles and active exhalation and should be measured during completely passive exhalation.

Total PEEP ($PEEP_{TOT}$) and *Intrinsic PEEP* ($PEEP_I$) are determined during an operator-initiated expiratory pause, in which the PSOL valves and exhalation valves are closed. $PEEP_{TOT}$ is the pressure measured during the pause maneuver. It is an estimate of the total pressure at the end of exhalation, referenced to atmosphere. $PEEP_I$ is an estimate of the pressure above the PEEP level at the end of exhalation.

Exhaled tidal volume (V_{TE}) is the volume exhaled from the patient’s lungs for a mandatory or spontaneous breath. It is computed by integrating the net flow over the expiratory period, then compliance- and BTPS compensating that value. The V_{TE} is computed based on a five-breath average. It is updated at the beginning of the next inspiratory phase.

V_{TE} is a basic indicator of the patient's ventilatory capacity and can be an indicator of the accuracy of the tidal volume setting for mandatory breaths.

Exhaled minute volume (VE_{TOT})is an estimate of the sum of volumes exhaled for mandatory and spontaneous breaths over the previous one-minute interval. VE_{TOT} is BTPS- and compliance-compensated. During the first minute of operation following power-up or a change to respiratory rate (f) or tidal volume (VT) settings, VE_{TOT} is updated at the beginning of each new inspiration or at ten-second intervals, whichever comes first. The ventilator uses this formula to compute VE_{TOT} based on up to eight breaths: VE_{TOT} = 60 x (total VT in t seconds)/t where t is the time in seconds since the computation started.

The VE_{TOT} computation is based on full and partial breaths that occurred during the preceding one-minute period. If the one-minute period includes a partial breath, then the interval is extended to include the entire breath, and the sum of all tidal volumes over this extended interval is normalized to one minute.

End expiratory flow (EEF) rate is the rate of expiratory flow that occurs at the end of exhalation and can be used to determine whether expiratory time is adequate to prevent gas trapping and intrinsic PEEP. The end expiratory flow rate is calculated as the expiratory flow that occurs when flow integration terminates during exhalation or when a new breath is initiated.

Supplemental figure 1: Study consort diagram

